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L16: Entry 1 of 14 File: USPT Jan 9, 2001

DOCUMENT-IDENTIFIER: US 6172042 B1
TITLE: Synthetic peptides that inhibit IL-6 activity

BSPR:
The present invention is based on the unexpected finding that short peptides within the IL-6 receptor gp80 molecule (IL-6R) could be defined by virtue of their ability to bind two different monoclonal antibodies (Mabs) which were previously known to strongly inhibit the activity of IL-6. Further, when chemically synthetized, in accordance with the present invention, these peptides when added to cultures of leukemic cells, were surprisingly shown to be capable of causing the complete inhibition of the growth of such leukemic (plasmacytoma/myeloma) cells.

BSPR:
Accordingly, the present invention provides a peptide or biologically active analogs thereof capable of inhibiting the activity of IL-6, wherein said peptide is characterized by being derived from the gp80 (IL-6R) subunit of the IL-6 receptor system and by being a linear epitope recognized by one or more monoclonal antibodies (Mab) specific to IL-6R, with the proviso that said peptide is other than the group of peptides consisting of: (i) the 16 amino acid peptide having the amino acid sequence of residues 249-264 of the IL-6R molecule; (ii) the 14 amino acid peptide having the amino acid sequence of residues 255-268 of the IL-6R molecule; (iii) the 6 amino acid peptide having the amino acid sequence of residues 249-254 of the IL-6R molecule; (iv) the 10 amino acid peptide having the amino acid sequence of residues 259-268 of the IL-6R molecule; and (v) the 10 amino acid peptide having the amino acid sequence of residues 249-258 of the IL-6R molecule.

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      FILE 'MEDLINE, BIOSIS' ENTERED AT 17:47:13 ON 02 FEB 2001
L1          2596 S ((INTERLEUKIN 6 RECEPTOR) OR (IL-6R) OR (IL-6 RECEPTOR) OR
(I
L2           638 S ANTIBOD###(S)L1
L3           156 S ANTI(A)L1
L4           652 S L2 OR L3
L5            11 S L4 AND CACHEXIA
L6             7 DUP REM L5 (4 DUPLICATES REMOVED)
L7           344 S GP80
L8           131 S ANTIBOD###(S)L7
L9            13 S ANTI(A)L7
L10          135 S L8 OR L9
L11            0 S L10 AND CACHEXIA
L12           22 S L10 AND EPITOPE#
L13           15 DUP REM L12 (7 DUPLICATES REMOVED)
L14         1938 S GP130
L15          481 S ANTIBOD###(S)L14
L16          127 S ANTI(A)L14
L17          495 S L15 OR L16
L18            1 S CACHEXIA AND L17
```

L7 ANSWER 3 OF 20 CANCERLIT
ACCESSION NUMBER: 96603660 CANCERLIT
DOCUMENT NUMBER: 96603660
TITLE: High levels of soluble **interleukin-6 receptor** (sIL-6R) and immunoreactive interleukin-6 (IL-6) predict poor prognosis in multiple myeloma (MM) (Meeting abstract).
AUTHOR: Pulkki K; Pelliniemi T T; Irjala K; Mattila K; Rajamaki A; Tienhaara A; Laakso M; Lahtinen R
CORPORATE SOURCE: Dept. of Clinical Chemistry, Turku Univ. Central Hosp., Turku, Finland.
SOURCE: Blood, **(1994)** 84 (10, Suppl 1) 385a.
ISSN: 0903-1936.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB IL-6 is a pleiotropic cytokine, which induces the proliferation of myeloma cells via the common signal transducer gp130 by binding to the membrane-bound or soluble alpha-chain of the IL-6 receptor. We have earlier demonstrated that serum concentration of immunoreactive IL-6 has prognostic significance in MM (Blood 82:262a, 1993). There is conflicting evidence on the significance of sIL-6R in MM. High **serum levels** of sIL-6R have been reported in MM patients (pts) compared to controls, but the levels have not reflected disease activity. On the other hand, serum sIL-6R has been reported to have independent prognostic significance in MM. In the present study we have analyzed the concentrations of IL-6 and sIL-6R in the sera of 207 MM pts at diagnosis (median age 68 yr, 26.7% in clinical stage I, 48.6% in stage II and 24.8% in stage III). IL-6 and sIL-6R were measured by sensitive ELISA methods. The upper reference limit for IL-6 was 3.2 ng/L and for sIL-6R 185 ug/L. **Serum** IL-6 **level** was raised in 42% and sIL-6R in 47% of the MM pts. The median value for IL-6 was 2.8 ng/L (range less than 0.4-107 ng/L) and for sIL-6R 173 ug/L (range 17-2116 ug/L). All pts were treated with intermittent melphalan and prednisone. At three yr 52% of the pts were alive. Pts surviving for three yr had significantly lower serum IL-6 and sIL-6R levels when compared to pts who died during the three-yr period (median values for IL-6 were 2.3 and 3.6 ng/L, respectively, p less than 0.001; and for sIL-6R 163 and 212 ug/L, respectively, p=0.0046, Mann-Whitney's U-test). There was no linear correlation between logarithmically transformed sIL-6R and IL-6 (r=0.008) or sIL-6R and serum beta 2-microglobulin, regarded as the most powerful single prognostic factor in MM (r=0.025). For survival analysis the pts were divided in four groups according to serum IL-6 and sIL-6R concentrations above/below the corresponding median values: 31% of those with both levels low (n=55), 51% of those with low IL-6 and high sIL-6R (n=49), 47% of those with high IL-6 and low sIL-6R (n=51) and 65% of those with both levels high (n=52) died during the three yr period. We conclude that serum IL-6 and sIL-6R concentrations have prognostic significance in MM. These two parameters do not correlate with each other. Combining the data of serum IL-6 and sIL-6R

concentrations at diagnosis might thus give further insights concerning the biology and prognosis of MM.

L7 ANSWER 4 OF 20 MEDLINE DUP

L7 ANSWER 3 OF 20 CANCERLIT
ACCESSION NUMBER: 96603660 CANCERLIT
DOCUMENT NUMBER: 96603660
TITLE: High levels of soluble **interleukin-6 receptor** (sIL-6R) and immunoreactive interleukin-6 (IL-6) predict poor prognosis in multiple myeloma (MM) (Meeting abstract).
AUTHOR: Pulkki K; Pelliniemi T T; Irjala K; Mattila K; Rajamaki A; Tienhaara A; Laakso M; Lahtinen R
CORPORATE SOURCE: Dept. of Clinical Chemistry, Turku Univ. Central Hosp., Turku, Finland.
SOURCE: Blood, **(1994)** 84 (10, Suppl 1) 385a.
ISSN: 0903-1936.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB IL-6 is a pleiotropic cytokine, which induces the proliferation of myeloma cells via the common signal transducer gp130 by binding to the membrane-bound or soluble alpha-chain of the IL-6 receptor. We have earlier demonstrated that serum concentration of immunoreactive IL-6 has prognostic significance in MM (Blood 82:262a, 1993). There is conflicting evidence on the significance of sIL-6R in MM. High **serum levels** of sIL-6R have been reported in MM patients (pts) compared to controls, but the levels have not reflected disease activity. On the other hand, serum sIL-6R has been reported to have independent prognostic significance in MM. In the present study we have analyzed the concentrations of IL-6 and sIL-6R in the sera of 207 MM pts at diagnosis (median age 68 yr, 26.7% in clinical stage I, 48.6% in stage II and 24.8% in stage III). IL-6 and sIL-6R were measured by sensitive ELISA methods. The upper reference limit for IL-6 was 3.2 ng/L and for sIL-6R 185 ug/L. **Serum** IL-6 **level** was raised in 42% and sIL-6R in 47% of the MM pts. The median value for IL-6 was 2.8 ng/L (range less than 0.4-107 ng/L) and for sIL-6R 173 ug/L (range 17-2116 ug/L). All pts were treated with intermittent melphalan and prednisone. At three yr 52% of the pts were alive. Pts surviving for three yr had significantly lower serum IL-6 and sIL-6R levels when compared to pts who died during the three-yr period (median values for IL-6 were 2.3 and 3.6 ng/L, respectively, p less than 0.001; and for sIL-6R 163 and 212 ug/L, respectively, p=0.0046, Mann-Whitney's U-test). There was no linear correlation between logarithmically transformed sIL-6R and IL-6 (r=0.008) or sIL-6R and serum beta 2-microglobulin, regarded as the most powerful single prognostic factor in MM (r=0.025). For survival analysis the pts were divided in four groups according to serum IL-6 and sIL-6R concentrations above/below the corresponding median values: 31% of those with both levels low (n=55), 51% of those with low IL-6 and high sIL-6R (n=49), 47% of those with high IL-6 and low sIL-6R (n=51) and 65% of those with both levels high (n=52) died during the three yr period. We conclude that serum IL-6 and sIL-6R concentrations have prognostic significance in MM. These two parameters do not correlate with each other. Combining the data of serum IL-6 and sIL-6R

concentrations at diagnosis might thus give further insights concerning the biology and prognosis of MM.

L7 ANSWER 4 OF 20 MEDLINE DU

L7 ANSWER 4 OF 20 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 95035857 MEDLINE
DOCUMENT NUMBER: 95035857 PubMed ID: 7948745
TITLE: Soluble **interleukin 6 receptor** in biological fluids from human origin.
AUTHOR: Frieling J T; Sauerwein R W; Wijdenes J; Hendriks T; van der Linden C J
CORPORATE SOURCE: Department of Surgery, University Hospital, Nijmegen, The Netherlands.
SOURCE: CYTOKINE, **(1994 Jul)** 6 (4) 376-81.
Journal code: 9005353. ISSN: 1043-4666.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19980206
Entered Medline: 19941220

AB OBJECTIVE: measurement of baseline soluble **interleukin 6 receptor** (sIL-6R) and interleukin 6 (IL-6) levels in biological fluids in non-pathological conditions. SUBJECTS AND MATERIALS: Blood and urine were obtained from healthy volunteers. Cerebrospinal fluid (CSF) and synovial fluid (SF) were obtained from patients during spinal puncture and athroscopy, respectively. Only CSF and SF of patients with proven non-pathological conditions were used in this study. Both sIL-6R and IL-6 were measured using ELISAs. It was shown that neither did sIL-6R interfere with the IL-6 ELISA nor did IL-6 interfere in the sIL-6R ELISA. Moreover, addition of recombinant sIL-6R to the IL-6 bio-assay (B9) did not influence IL-6 recovery. RESULTS: using our sIL-6R ELISA we found baseline levels for sIL-6R in serum of 76.6 +/- 19.3 ng/ml in serum and 3.7 +/- 1.3 ng/ml in urine. In non-pathological conditions sIL-6R concentrations in CSF are 1.6 +/- 0.4 ng/ml, and in SF 11.6 +/- 3.3 ng/ml, while IL-6 concentrations are below detectable ranges in these fluids. CONCLUSIONS: sIL-6R **levels** are detectable in **serum**, urine, CSF and SF during non-pathological conditions. sIL-6R **levels** in **serum** outrange **levels** in CSF, urine and SF and large interindividual differences in baseline concentrations for sIL-6R exist.

L7 ANSWER 5 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRA

L7 ANSWER 11 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 93209277 MEDLINE
DOCUMENT NUMBER: 93209277 PubMed ID: 8458373
TITLE: Increased and highly stable levels of functional soluble **interleukin-6 receptor** in sera of patients with monoclonal gammopathy.
AUTHOR: Gaillard J P; Bataille R; Brailly H; Zuber C; Yasukawa K; Attal M; Maruo N; Taga T; Kishimoto T; Klein B
CORPORATE SOURCE: Laboratory of Immunological and Hematological Oncology, Institut de Biologie, Nantes, France.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, **(1993 Apr)** 23 (4) 820-4.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930514
Last Updated on STN: 19980206
Entered Medline: 19930423

AB Soluble human **interleukin-6 receptor** (sIL-6R) was measured in the serum of 30 healthy individuals, 32 individuals with monoclonal gammopathy of undetermined significance (MGUS), 20 patients with early multiple myeloma (MM) and 54 patients with overt MM. The serum activity recognized by an immunoradiometric assay was determined to be sIL-6R, because of its binding capacity to IL-6 and its molecular mass of 55 kDa. All sera of healthy individuals contained sIL-6R (mean value: 89 ng/ml, range 17-300 ng/ml). **Serum** sIL-6R **levels** were increased by 51% in patients with MGUS (mean value: 135 ng/ml, $p < 0.005$), by 44% in patients with early myeloma (mean value: 128 ng/ml, $p < 0.001$) and by 116% in patients with overt MM (mean value: 193 ng/ml, $p < 0.001$). In patients with MM, a complete lack of correlation ($p > 0.7$) was found between **serum** sIL-6R **levels** and other previously recognized prognostic factors in this disease, particularly **serum** IL-6 **levels** and those factors related to tumor cell mass. The independence of **serum** sIL-6R **levels** on tumor cell mass was directly demonstrated by studying four patients with MM treated with autologous bone marrow transplantation for periods of between 320 and 760 days. These levels were found to be remarkably stable and constant, independent of whether patients relapsed or achieved complete remission. Finally, physiological concentrations of sIL-6R were found to increase by tenfold the sensitivity of human myeloma cell lines to IL-6. These observations suggest a high control of the sIL-6R level in vivo, and, possibly, an important functional role of this circulating protein in patients with monoclonal gammopathies.

L4 ANSWER 1 OF 2 LIFESCI COPYRIGHT 2002 CSA
ACCESSION NUMBER: 95:91383 LIFESCI
TITLE: Serum soluble interleukin 6 (IL-6) receptor and IL-6/soluble IL-6 receptor complex in systemic juvenile rheumatoid arthritis
AUTHOR: De Benedetti, F.; Massa, M.; Pignatti, P.; Albani, S.; Novick, D.; Martini, A.*
CORPORATE SOURCE: Clin. Pediatr., IRCCS San Matteo, P. le Golgi 2, 27100 Pavia, Italy
SOURCE: J. CLIN. INVEST., (**1994**) vol. 93, no. 5, pp. 2114-2119.
ISSN: 0021-9738.
DOCUMENT TYPE: Journal
FILE SEGMENT: F
LANGUAGE: English
SUMMARY LANGUAGE: English

AB By using a sandwich ELISA, soluble human IL-6 receptor (sIL-6 R) levels were measured in the sera of 20 healthy children and of 25 patients with systemic juvenile rheumatoid arthritis (JRA). In patients with systemic JRA, serum sIL-6 R levels (114.6 plus or minus 37.7 ng/ml) were significantly lower than those of healthy children (161.2 plus or minus 45.5 ng/ml). Serum sIL-6 R levels were negatively correlated (r = -0.610) with serum IL-6 levels measured with the B9 cells. The serum IL-6/sIL-6 R complex was detected using an ELISA based on a monoclonal antibody to IL-6 for capture and on a monoclonal antibody to human sIL-6 R for detection. Healthy controls had little, if any, detectable serum IL-6/sIL-6 R complex (OD 0.024 plus or minus 0.027), while the majority of patients with systemic JRA presented measurable serum IL-6/sIL-6 R complex (OD 0.492 plus or minus 0.546). IL-6 **levels** estimated in the **circulating** IL-6/sIL-6 R complexes were in the range of nanograms per milliliter and similar to 20-fold higher than those measured by the B9 cells. Since serum C-reactive protein concentrations were much more correlated with serum levels of IL-6/sIL-6 R complexes (r = 0.713, r super(2) = 0.51) than with the serum IL-6 levels measured with the B9 cells (r = 0.435, r super(2) = 0.19), the large quantities of serum IL-6 present in IL-6/sIL-6 R complexes appear to be biologically relevant in vivo, at least as far as the induction by IL-6 of acute phase protein production. (DBO)

L18 ANSWER 1 OF 1 MEDLINE
ACCESSION NUMBER: 1999271363 MEDLINE
DOCUMENT NUMBER: 99271363
TITLE: Advances in interleukin-6 therapy.
AUTHOR: Ogata A; Nishimoto N; Yoshizaki K
CORPORATE SOURCE: Second Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya.
SOURCE: RINSHO BYORI. JAPANESE JOURNAL OF CLINICAL PATHOLOGY, (1999 Apr) 47 (4) 321-6. Ref: 12
Journal code: KIV. ISSN: 0047-1860.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: Japanese
ENTRY MONTH: 199908
ENTRY WEEK: 19990804

AB Interleukin-6 (IL-6) exhibits multiple biologic activities such as regulation of immunological responses and hematopoiesis, promotion of acute inflammation, and stimulation of some malignant and non-malignant cell growth. The IL-6 receptor system consists of an IL-6 specific binding molecule, IL-6R and a signal transducer, **gp130**. Following **gp130** dimerization, IL-6 activates multiple signaling pathways (Ras dependent MAPk cascade, STAT1-STAT3 heterodimer pathway, and STAT3 homodimer pathway). Several other cytokines including oncostatin M, IL-11, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and cardiotropin-1 (CT-1) use **gp130** as a common signal transducing molecule and therefore have similar biological activities. Two major in vivo functions of IL-6 are reported. Firstly, IL-6 acts as a growth factor of some malignant and non-malignant cells such as malignant plasma cells in multiple myeloma, mesangial cells in the kidney, and keratinocytes. Secondly, IL-6 mediates inflammatory and immune responses in rheumatoid arthritis, Castleman disease, psoriasis, cardiac myxoma, **cachexia**, and other inflammatory conditions. Recently, a humanized anti-IL-6 receptor **antibody** was developed. Neutralization of IL-6 activity by the humanized anti-IL-6 receptor **antibody** may be a new therapeutic approach for IL-6 related diseases such as multiple myeloma, Castleman disease and rheumatoid arthritis.

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                  Substances (PICCS) has been added to CHEMLIST
 NEWS  3  Oct 27  New Extraction Code PAX now available in Derwent
                  Files
 NEWS  4  Oct 27  SET ABBREVIATIONS and SET PLURALS extended in
                  Derwent World Patents Index files
 NEWS  5  Oct 27  Patent Assignee Code Dictionary now available
                  in Derwent Patent Files
 NEWS  6  Oct 27  Plasdoc Key Serials Dictionary and Echoing added to
                  Derwent Subscriber Files WPIDS and WPIX
 NEWS  7  Nov 29  Derwent announces further increase in updates for DWPI
 NEWS  8  Dec  5  French Multi-Disciplinary Database PASCAL Now on STN
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 NEWS 11  Dec 17  Merged CEABA-VTB for chemical engineering and
                  biotechnology
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 NEWS 13  Dec 17  SYNTHLINE from Prous Science now available on STN
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FILE 'HOME' ENTERED AT 17:46:12 ON 02 FEB 2001

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(Il-6 R))

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L23 ANSWER 2 OF 4 MEDLINE
ACCESSION NUMBER: 1998055693 MEDLINE
DOCUMENT NUMBER: 98055693
TITLE: Analysis of the mechanism of action of anti-human interleukin-6 and anti-human interleukin-6 receptor-neutralising monoclonal antibodies.
AUTHOR: Kalai M; Montero-Julian F A; Brakenhoff J P; Fontaine V; De
Wit L; Wollmer A; Brailly H; Content J; Grotzinger J
CORPORATE SOURCE: Institut Pasteur de Bruxelles, Departement de Virologie, Belgium.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1997 Nov 1) 249 (3) 690-700.
Journal code: EMZ. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199803
ENTRY WEEK: 19980303

AB Anti-human interleukin-6 (human **IL-6**) and anti-human **IL-6** receptor (IL-6R)-neutralising monoclonal **antibodies** (mAbs) are among the most promising human **IL-6**-specific inhibitors and have been shown to exert short-term beneficial effects in clinical trials. Simultaneous treatment with different anti-human **IL-6** or anti-human IL-6R mAbs was recently suggested to be a potent way to inhibit the action of the cytokine in vivo. Although some of these mAbs are already used, their mechanisms of action and the location of their **epitopes** on the surface of human **IL-6** and human IL-6R are still unknown. Here, we analysed the capacity of several anti-human **IL-6** and anti-human IL-6R mAbs to inhibit the interaction between human **IL-6**, human IL-6R, and human glycoprotein 130 (**gp130**). We mapped the **epitopes** of several of these mAbs by studying their binding to human **IL-6** and human IL-6R mutant proteins. Our results show that several anti-human **IL-6** and anti-human IL-6R-neutralising mAbs block the binding between human **IL-6** and human IL-6R, whereas others block the binding to **gp130**. We provide evidence that some of the latter mAbs inhibit interaction with gp130beta1, whereas others interfere with the binding to gp130beta2. Our results suggest that residues included in the C'D' loop of human IL-6R interact with gp130beta2.

L

L23 ANSWER 3 OF 4 MEDLINE
ACCESSION NUMBER: 97266589 MEDLINE
DOCUMENT NUMBER: 97266589
TITLE: Specific inhibition of **IL-6** signalling with monoclonal **antibodies** against the **gp130** receptor.
AUTHOR: Liautard J; Sun R X; Cotte N; Gaillard J P; Mani J C; Klein B; Brochier J
CORPORATE SOURCE: INSERM U291, Montpellier, France.
SOURCE: CYTOKINE, (1997 Apr) 9 (4) 233-41.
Journal code: A52. ISSN: 1043-4666.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY WEEK: 19970804

AB A family of cytokines [**IL-6**, IL-11, oncostatin M (OM), leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and cardiotrophin-1] involved in various inflammatory or tumoral diseases share the same gp130 signal transducer chain. The complex formed with their specific receptors associates with a common transducing gp130 membrane protein (gp130) resulting in the formation of high avidity receptor and activation of tyrosine kinases. With the view of identifying gp130 domains specifically involved in **IL-6** signalling, the authors prepared 37 new **anti-gp130** mAb and analysed the structure-function relationship of the molecule. By cross-competition ELISA, the mAb were classified in 10 subgroups called A to J. By ELISA and BIAcore analysis, the mAb were found to recognize at least 18 antigenic specificities of the gp130 chain. The mAb reacted against the soluble and the membrane forms of gp130 as well. Their ability to inhibit the proliferation of the human myeloma cell line XG-4 of which the growth is strictly dependent on the presence of either exogenous **IL-6**, or LIF, or OM, or CNTF was studied. Besides mAb with no evident neutralizing effect (G and H) and mAb which neutralized equally well the activity of all tested cytokines (all mAb of groups A, I and J), some showed a selective effect. Those of group F inhibited also the proliferation induced by the 4 cytokines, but more specifically that dependent on the CNTF. mAb of groups B and E specifically inhibited the growth induced by **IL-6**, whereas those of group C inhibited that induced by LIF and OM. These results show the presence of different gp130 **epitopes** specifically involved in the signaling induced by the cytokines of the gp130 family. In ELISA, only mAb of group B and E were found to inhibit the binding of the **IL-6** -IL-6R complex to gp130, showing that they identified one or two domains of gp130 involved in its interaction with the **IL-6** -IL-6R complex. Precise identification of this(ese) **epitope**(s) would be useful to better understand the mechanisms of the **IL-6** signalling.

L13 ANSWER 1 OF 15 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97067803 MEDLINE
DOCUMENT NUMBER: 97067803
TITLE: Identification of a novel antigenic structure of the human receptor for interleukin-6 involved in the interaction with the glycoprotein 130 chain.
AUTHOR: Gaillard J P; Liautard J; Mani J C; Fernandez Suarez J M; Klein B; Brochier J
CORPORATE SOURCE: INSERM U291, Montpellier, France.
SOURCE: IMMUNOLOGY, (1996 Sep) 89 (1) 135-41.
Journal code: GH7. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199702

AB The receptor for interleukin-6 (IL-6) is characterized by a ligand-binding glycoprotein 80 (**gp80**) transmembrane chain (IL-6R) which associates with a signal-transducer gp130 chain. We previously raised a series of monoclonal **antibodies** (mAb) recognizing different **epitopes** of the human IL-6R and interfering with the function of the receptor. One of them, M182, was able to diminish the proliferation of IL-6-dependent plasmacytoma cell lines although it was found unable to inhibit the binding of IL-6 to its receptor. Using an enzyme-linked immunosorbent assay for measuring the binding of IL-6 IL-6R to the gp130 chain, we showed that M182 was directed against a structure directly involved in the IL-6R gp130 interaction. M182 was able to potentiate the inhibitor effect of anti-IL-6R mAB which interfere with the binding of IL-6, leading to complete inhibition of the proliferation of IL-6-dependent cell lines. M182 was also found to synergize with inhibitory anti-IL-6 mAb. Therefore this structure appears to be an important regulatory domain of the IL-6R and a valuable target for inhibiting IL-6 signalling.

L13 ANSWER 4 OF 15 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 95244774 MEDLINE
DOCUMENT NUMBER: 95244774
TITLE: IL-6-induced changes in synthesis of alpha 1-acid glycoprotein in human hepatoma Hep3B cells are distinctively regulated by monoclonal **antibodies** directed against different **epitopes** of IL-6 receptor (**gp80**).
AUTHOR: Daveau M; Liautard J; Gaillard J P; Hiron M; Brochier J; Lebreton J P
CORPORATE SOURCE: INSERM Unite 78, Bois-Guillaume, France.
SOURCE: EUROPEAN CYTOKINE NETWORK, (1994 Nov-Dec) 5 (6) 601-8. Journal code: A56. ISSN: 1148-5493.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508

AB The synthesis of the human acute-phase alpha 1-acid glycoprotein (AGP) is primarily controlled by IL-6 and IL-1 in liver cells. In the present study, monoclonal **antibodies** against human **gp80** interleukin-6 receptor (IL-6R) were utilized to study the role of the IL-6R in the control of the IL-6-induced AGP synthesis in the human hepatoma Hep3B cell line. Two of the 4 MAbs used in this study, M164 and M195, identified 2 different **epitopes** involved in IL-6 binding and two others, M91 and M182, recognized **epitopes** not involved in IL-6 binding. Dose-response experiments indicated that up to 55% of AGP synthesis was inhibited by 10(5) ng/ml of MAbs 164 or 195 when Hep3B cells were treated by IL-6 for 48h. Kinetics of the inhibition of AGP synthesis after addition of anti-IL-6R indicated that the decrease of the IL-6-induced AGP synthesis by Hep3B cells was obtained immediately after the addition of the anti-IL-6R MAbs. Of the two MAbs not involved in IL-6 binding, M91 was unable to interfere with the IL-6-induced AGP synthesis whereas, surprisingly, M182 decreased it by about 25%. Since M182 was also able to interfere with the proliferative response of an IL-6 dependent plasma cell line, our results suggested that M182 may be directed to a structure involved in the IL-6/IL-6R gp130 complex formation. (ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 5 OF 15 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 95035879 MEDLINE
DOCUMENT NUMBER: 95035879
TITLE: **Epitope** analysis of human IL-6 receptor **gp80** molecule with monoclonal **antibodies**.
AUTHOR: Liautard J; Gaillard J P; Mani J C; Montero-Julian F; Duperray C; Lu Z Y; Jourdan M; Klein B; Brailly H; Brochier J
CORPORATE SOURCE: INSERM U291, Montpellier, France.
SOURCE: EUROPEAN CYTOKINE NETWORK, (1994 May-Jun) 5 (3) 293-300. Journal code: A56. ISSN: 1148-5493.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502

AB **Gp80** human IL-6R was studied using 7 murine mAb (M37, M91, M113, M139, M164, M182 and M195) obtained after fusion of splenocytes of Balb/c mice immunised with a mixture of recombinant IL-6 receptor (rIL-6R) and cells from 2 cell lines expressing IL-6R. These were U266, which is IL-6 independent and XG-1 which is IL-6-dependent. In ELISA the 7 mAb reacted against the rIL-6R and against the natural soluble form found in plasma (nIL-6R), which both lack transmembrane and cytoplasmic domains. However, M195 reacted less with the natural than with the recombinant soluble IL-6R. Using FACS analysis, the 7 mAb were shown to bind to U266 cells but not to the Namalva cell line which is deprived of IL-6R. This showed that they all recognised the membrane form of the IL-6R. Three of the anti-IL-6R mAb reacted with rIL-6R by Western blotting. Four different **epitopes** of the molecule were identified, either by cross-blocking experiments of mAb binding to IL6R in ELISA or by the biosensor Biacore technology. A group of 4 mAb (M37, M113, M139 and M164) and another mAb (M195) identified 2 different **epitopes** involved in IL-6 binding. These **antibodies** were able to inhibit the binding of IL-6 to IL-6R and the proliferation of the IL-6-dependent XG-1 cell line. M91 and M182 recognized 2 other **epitopes** that were not involved in IL-6 binding. As expected, M91 did not inhibit XG-1 proliferation; in contrast, M182 interfered with the proliferative response of the XG-1 cell line.(ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:91564 BIOSIS
DOCUMENT NUMBER: PREV199497104564
TITLE: Structural and functional studies of the human **gp80** interleukin-6 receptor (IL-6R) with monoclonal **antibodies** (MAb.
AUTHOR(S): Liautard, J. (1); Gaillard, J. P. (1); Mani, J. C.; Montero-Julian, F. A.; Duperray, C. (1); Klein, B.; Brailly, H.; Brochier, J. (1)
CORPORATE SOURCE: (1) INSERM U291, 99 Rue Puech Villa, 34197 Montpellier Cedex 05 France
SOURCE: Tissue Antigens, (1993) Vol. 42, No. 4, pp. 330.
Meeting Info.: 5th International Conference on Human Leukocyte Differentiation Antigens Boston, Massachusetts, USA November 3-7, 1993
ISSN: 0001-2815.
DOCUMENT TYPE: Conference
LANGUAGE: English

L13 ANSWER 7 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:91562 BIOSIS
DOCUMENT NUMBER: PREV199497104562
TITLE: Analysis of monoclonal **antibodies** (MAb) against human **GP80** interleukin-6-receptor (IL-6R.
AUTHOR(S): Gaillard, J. P.; Liautard, J.; Duperray, C.; Brochier, J.
CORPORATE SOURCE: INSERM, U291, 99 rue Puech Villa, 34197 Montpellier Cedex 5
France
SOURCE: Tissue Antigens, (1993) Vol. 42, No. 4, pp. 330.
Meeting Info.: 5th International Conference on Human Leukocyte Differentiation Antigens Boston, Massachusetts, USA November 3-7, 1993
ISSN: 0001-2815.
DOCUMENT TYPE: Conference
LANGUAGE: English

In 5 patients, the lymphoma progressed during treatment. Among them were the 2 patients in whom endogenous IL-6 effect was not neutralized. Five patients experienced a stabilization, and 1 a partial remission. This effect on lymphoma growth lasted for 8 to 28 weeks. The anti-IL-6 MoAb had a clear effect on lymphoma-associated fever and **cachexia**. The mean body weight increase was 1.4 +/- 0.5 kg between day 1 and day 21, and reached 12 kg in 120 days in 1 patient who received three courses of treatment. Side effects were a consistent but moderate thrombocytopenia, and an occasional and moderate decrease of neutrophil counts. Immunization against the MoAb was observed in only 2 patients. These results indicate that in some cases of lymphomas growth of malignant cells may be partially IL-6-dependent and that neutralizing endogenous effect of IL-6 completely abrogates B clinical symptoms.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	6.38	6.68

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 17:49:19 ON 02 FEB 2001

ACCESSION NUMBER: 1998029492 MEDLINE
DOCUMENT NUMBER: 98029492
TITLE: Inhibition of experimental cancer **cachexia** by anti-cytokine and anti-cytokine-receptor therapy.
AUTHOR: Strassmann G; Kambayashi T
CORPORATE SOURCE: Department of Immunology, Otsuka-America Pharmaceuticals, Inc, Rockville, MD 20850, USA.
SOURCE: CYTOKINES AND MOLECULAR THERAPY, (1995 Jun) 1 (2) 107-13. Ref: 70
Journal code: CN2. ISSN: 1355-6568.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY WEEK: 19980204

AB **Cachexia** consists of a constellation of metabolic changes that occur in cancer patients, including the reduction of muscle and fat tissue, asthenia, anorexia, hypoglycemia and hypercalcemia. These syndromes complicate therapeutic intervention and decrease the quality of life of the patient. This review discusses the involvement of cytokines in cancer **cachexia** and describes the contribution of IL-6 and other cytokines to the wasting of C-26-bearing mice. The neutralization of IL-6 by **antibody**, or **IL-6 receptor** antagonism by suramin, significantly reduce the severity of key parameters of **cachexia**. The participation of several other factors (PGE2, IL-1, IL-10 and TNF-alpha) in the cellular communication between the C-26 tumor cell and tumor-infiltrating macrophages is also described.

L6 ANSWER 7 OF 7 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 95002966 MEDLINE
DOCUMENT NUMBER: 95002966
TITLE: Administration of an anti-interleukin-6 monoclonal antibody to patients with acquired immunodeficiency syndrome and lymphoma: effect on lymphoma growth and on B clinical symptoms.
AUTHOR: Emilie D; Wijdenes J; Gisselbrecht C; Jarrousse B; Billaud E; Blay J Y; Gabarre J; Gaillard J P; Brochier J; Raphael M
CORPORATE SOURCE: INSERM U131, Hopital Antoine Becl`ere, Clamart, France.
SOURCE: BLOOD, (1994 Oct 15) 84 (8) 2472-9.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199501

AB Increased interleukin-6 (IL-6) production and expression by malignant cells of the **IL-6 receptor** has been evidenced in a subgroup of non-Hodgkin's lymphomas, suggesting that this cytokine plays a role in lymphoma growth and in B clinical symptoms. In this study, the effect of the administration of an anti-IL-6 monoclonal **antibody** (MoAb) was analyzed in 11 patients seropositive for human immunodeficiency virus-1 and suffering from an immunoblastic or a polymorphic large-cell lymphoma. The **antibody** (BE-8, 10 to 40 mg/day) was administered for 21 days. Neutralization of in vivo IL-6 effect was assessed by monitoring C-reactive protein levels in the serum.

ENTRY MONTH: 199703
ENTRY WEEK: 19970301
AB Progression of skeletal muscle atrophy is one of the characteristic features in cancer patients. Interleukin-6 (IL-6) has been reported to be responsible for the loss of lean body mass during cancer **cachexia** in colon-26 adenocarcinoma (C-26)-bearing mice. This study was carried out to elucidate the intracellular proteolytic pathways operating in skeletal muscle in C-26-bearing mice, and to examine the effect of **anti IL-6 receptor antibody** on muscle atrophy. On day 17 after tumor inoculation, the gastrocnemius muscle weight of C-26-bearing mice had significantly decreased to 69% of that of the pair-fed control mice. This weight loss occurred in association with increases in the mRNA levels of cathepsins B and L, poly-ubiquitin (Ub) and the subunits of proteasomes in the muscles. Furthermore, enzymatic activity of cathepsin B+L in the muscles also increased to 119% of the control. The administration of anti-murine **IL-6 receptor antibody** to C-26-bearing mice reduced the weight loss of the gastrocnemius muscles to 84% of that of the control mice, whose enzymatic activity of cathepsin B+L and mRNA levels of cathepsin L and poly-Ub were significantly suppressed compared with those of the C-26-bearing mice. Our data indicate that both the lysosomal cathepsin pathway and the ATP-dependent proteolytic pathway might be involved in the muscle atrophy of C-26-bearing mice. The results also suggest that **anti IL-6 receptor antibody** could be a potential therapeutic agent against muscle atrophy in cancer **cachexia** by inhibiting these proteolytic systems.

L6 ANSWER 5 OF 7 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 96133540 MEDLINE
DOCUMENT NUMBER: 96133540
TITLE: **Interleukin 6 receptor antibody** inhibits muscle atrophy and modulates proteolytic systems in interleukin 6 transgenic mice.
AUTHOR: Tsujinaka T; Fujita J; Ebisui C; Yano M; Kominami E; Suzuki K; Tanaka K; Katsume A; Ohsugi Y; Shiozaki H; Monden M
CORPORATE SOURCE: Department of Surgery II, Osaka University Medical School, Suita, Japan.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1996 Jan 1) 97 (1) 244-9.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199604
AB The muscles of IL-6 transgenic mice suffer from atrophy. Experiments were carried out on these transgenic mice to elucidate activation of proteolytic systems in the gastrocnemius muscles and blockage of this activation by treatment with the anti-mouse **IL-6 receptor** (mIL-6R) **antibody**. Muscle atrophy observed in 16-wk-old transgenic mice was completely blocked by treatment with the mIL-6R **antibody**. In association with muscle atrophy, enzymatic activities and mRNA levels of cathepsins (B and L) and mRNA levels of ubiquitins (poly- and mono-ubiquitins) increased, whereas the mRNA level of muscle-specific calpain (calpain 3) decreased. All these changes were completely eliminated by treatment with the mIL-6R **antibody**. This **IL-6 receptor antibody** could, therefore, be effective against muscle wasting in sepsis and cancer **cachexia**, where IL-6 plays an important role.

L6 ANSWER 6 OF 7 MEDLINE

Mundy G R; Yoneda T
CORPORATE SOURCE: Department of Medicine, University of Texas Health Science Center, San Antonio, USA.
CONTRACT NUMBER: CA-40035 (NCI)
DK-45229 (NIDDK)
AR-39529 (NIAMS)
+
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1996 Jul) 11 (7) 905-11.
Journal code: 130. ISSN: 0884-0431.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702

AB Interleukin-6 (IL-6) is a multifunctional cytokine that is produced not only by a variety of normal cells but also by cancer cells. IL-6 produced by cancer cells stimulates the proliferation of these cancer cells in an autocrine/ paracrine manner and causes paraneoplastic syndromes including hypercalcemia, **cachexia**, and leukocytosis. We have reported previously that a human oral squamous cancer associated with hypercalcemia produces large amounts of IL-6, that animals bearing this cancer exhibit elevated levels of plasma IL-6, and that neutralizing **antibodies** to human IL-6 reverse hypercalcemia in tumor-bearing animals, indicating an important role of IL-6 in the hypercalcemia in this model. Because these cancer cells overexpress epidermal growth factor receptors (EGFR) with intrinsic tyrosine kinase (TK) activity similar to many other squamous cancers, we examined the effects of herbimycin A, a tyrosine kinase inhibitor, on IL-6 production and hypercalcemia in animals bearing this cancer to develop a new approach to treat the hypercalcemia associated with malignancy. Intraperitoneal administration (once a day for 2 days) of herbimycin A to cancer-bearing hypercalcemic mice reduced the plasma levels of human IL-6 and impaired the hypercalcemia. During 2-day treatment with herbimycin A, no changes were observed in tumor size. Of interest, plasma levels of mouse, but not human, soluble **IL-6 receptors** were also elevated. However, herbimycin A showed no effects on plasma levels of mouse soluble **IL-6 receptors**. Herbimycin A suppressed the tyrosine autophosphorylation of EGFR and IL-6 mRNA expression and production, all of which were stimulated by EGF. The data raise the possibility that TK inhibitors may be potential mechanism-based therapeutic agents for the treatment of hypercalcemia associated with squamous cancers which overexpress EGFR.

L6 ANSWER 4 OF 7 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97092727 MEDLINE
DOCUMENT NUMBER: 97092727
TITLE: **Anti-interleukin-6 receptor antibody** prevents muscle atrophy in colon-26 adenocarcinoma-bearing mice with modulation of lysosomal and ATP-ubiquitin-dependent proteolytic pathways.
AUTHOR: Fujita J; Tsujinaka T; Yano M; Ebisui C; Saito H; Katsume A; Akamatsu K; Ohsugi Y; Shiozaki H; Monden M
CORPORATE SOURCE: Department of Surgery II, Osaka University Medical School, Japan.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1996 Nov 27) 68 (5) 637-43.
Journal code: GQU. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals

regulation of immunological responses and hematopoiesis, promotion of acute inflammation, and stimulation of some malignant and non-malignant cell growth. The **IL-6 receptor** system consists of an IL-6 specific binding molecule, **IL-6R** and a signal transducer, gp130. Following gp130 dimerization, IL-6 activates multiple signaling pathways (Ras dependent MAPk cascade, STAT1-STAT3 heterodimer pathway, and STAT3 homodimer pathway). Several other cytokines including oncostatin M, IL-11, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and cardiotropin-1 (CT-1) use gp130 as a common signal transducing molecule and therefore have similar biological activities. Two major in vivo functions of IL-6 are reported. Firstly, IL-6 acts as a growth factor of some malignant and non-malignant cells such as malignant plasma cells in multiple myeloma, mesangial cells in the kidney, and keratinocytes. Secondly, IL-6 mediates inflammatory and immune responses in rheumatoid arthritis, Castleman disease, psoriasis, cardiac myxoma, **cachexia**, and other inflammatory conditions. Recently, a humanized **anti-IL-6 receptor antibody** was developed. Neutralization of IL-6 activity by the humanized **anti-IL-6 receptor antibody** may be a new therapeutic approach for IL-6 related diseases such as multiple myeloma, Castleman disease and rheumatoid arthritis.

L6 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:403229 BIOSIS
DOCUMENT NUMBER: PREV199799709432
TITLE: Experimental study of the effect of IL-6 on cancer **cachexia**.
AUTHOR(S): Ikeda, Teruyoshi; Nishiguchi, Yukio (1); Chung, Yong-Suk; Yamada, Nobuya; Sowa, Michio
CORPORATE SOURCE: (1) First Dep. Surgery, Osaka City Univ., Med. Sch., 1-5-7 Asahimachi, Abeno-ku, Osaka 545 Japan
SOURCE: Oncology Reports, (1997) Vol. 4, No. 5, pp. 921-926. ISSN: 1021-335X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Several cytokines, including IL-1, TNF, LIF and IL-6 have recently been proposed as **cachexia** inducers. We experimentally examined the participation of cytokines, particularly, IL-6, in cancer **cachexia** using the human digestive cancer cell lines MKN 28, MKN 45, MKN 74, Kato-III, OCUM-2M (gastric cancer), SW1990, Panc-1 (pancreatic cancer), and OCUG (gallbladder cancer). A high level of IL-6 was detected in the OCUG culture medium. Nude mice bearing OCUG tumor had reduced body weight even when the tumor was relatively small. Loss of both muscle and adipose tissue, anemia, hypoglycemia, and a high serum level of human IL-6 were observed in these mice. However, body weight recovered rapidly to the level of that of nontumor-bearing mice after resection of OCUG tumor. Antihuman IL-6 but not anti-murine **IL-6 receptor antibodies** significantly suppressed the development of **cachexia** as measured by various indicators of **cachexia** including loss of both muscle and adipose tissue, anemia and hypoglycemia, as well as weight loss. These results suggest that OCUG-bearing mice exhibited cancer **cachexia** mediated by IL-6, and that of OCUG cell line might be useful as a human digestive cancer **cachexia** model.

L6 ANSWER 3 OF 7 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 96390016 MEDLINE
DOCUMENT NUMBER: 96390016
TITLE: Herbimycin A, a tyrosine kinase inhibitor, impairs hypercalcemia associated with a human squamous cancer producing interleukin-6 in nude mice.
AUTHOR: Moriyama K; Williams P J; Niewolna M; Dallas M R; Uehara Y;

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L1 2596 ((INTERLEUKIN 6 RECEPTOR) OR (IL-6R) OR (IL-6 RECEPTOR) OR (IL6R
) OR (IL-6 R))

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L2 638 ANTIBOD###(S) L1

=> s anti(a)l1

L3 156 ANTI(A) L1

=> s l2 or l3

L4 652 L2 OR L3

=> s l4 and cachexia

L5 11 L4 AND CACHEXIA

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L6 7 DUP REM L5 (4 DUPLICATES REMOVED)

=> d ibib abs tot

L6 ANSWER 1 OF 7 MEDLINE
ACCESSION NUMBER: 1999271363 MEDLINE
DOCUMENT NUMBER: 99271363
TITLE: Advances in interleukin-6 therapy.
AUTHOR: Ogata A; Nishimoto N; Yoshizaki K
CORPORATE SOURCE: Second Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya.
SOURCE: RINSHO BYORI. JAPANESE JOURNAL OF CLINICAL PATHOLOGY, (1999
Apr) 47 (4) 321-6. Ref: 12
Journal code: KIV. ISSN: 0047-1860.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: Japanese
ENTRY MONTH: 199908
ENTRY WEEK: 19990804
AB Interleukin-6 (IL-6) exhibits multiple biologic activities such as

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Related Articles

TITLE:	**Monoclonal antibodies define different functional epitopes on gp130 signal transducer.**
AUTHORS:	**Chevalier S; Clement C; Robledo O; Klein B; Gascan H; Wijdenes J**
AUTHOR AFFILIATION:	**INSERM U298, CHRU Angers, France.**
SOURCE:	**Ann N Y Acad Sci 1995 Jul 21;762:482-4**
CITATION IDS:	**PMID: 7668565 UI: 95398146**
MAIN MESH HEADINGS:	**Antibodies, Monoclonal/*immunology Membrane Glycoproteins/*immunology**
ADDITIONAL MESH HEADINGS:	**Animal Epitope Mapping Human Interleukin-6/metabolism Mice Mice, Inbred BALB C 1995/07 1995/21 00:00**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
CAS REGISTRY NUMBERS:	**0 (Antibodies, Monoclonal) 0 (Interleukin-6) 0 (Membrane Glycoproteins) 133483-10-0 (gp130 signal transducer)**
LANGUAGES:	**Eng**

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Related Articles

TITLE: Interleukin-6 signal transducer gp130 has specific binding sites for different cytokines as determined by antagonistic and agonistic anti-gp130 monoclonal antibodies.

AUTHORS: Wijdenes J; Heinrich PC; Muller-Newen G; Roche C; Gu ZJ; Clement C; Klein B

AUTHOR AFFILIATION: Diaclone, Besancon, France.

SOURCE: Eur J Immunol 1995 Dec;25(12):3474-81

CITATION IDS: PMID: 8566040 UI: 96140689

ABSTRACT: The cytokines interleukin (IL)-6, IL-11, ciliary neurotrophic factor (CNTF), leukemia inhibitor factor (LIF), oncostatin M (OSM) and probably the recently cloned cytokine cardiotrophin-1, signal, in combination with their specific receptors, through the common signal transducer gp130. Here, we report that the signaling activities of IL-6, IL-11, CNTF and OSM/LIF can be specifically blocked by different anti-gp130 monoclonal antibodies (mAb). Furthermore, we found two mAb, B-P8 and B-S12, which directly activate gp130 independently of the presence of cytokines or their receptors. This agonistic activity includes induction of cytokine-dependent cell proliferation and stimulation of acute-phase protein synthesis in liver cells. Compared to B-P8 mAb, the B-S12 mAb exhibited the strongest agonistic activity, while both mAb are synergistic in their action. This activity could not be blocked by inhibiting mAb against IL-6 and the IL-6 receptor. In contrast to F(ab')2 of B-S12 which still could activate gp130, Fab fragments completely lost their agonistic activity. Activation by tyrosine phosphorylation of the transcription factors Stat1 and APRF/Stat3 was also induced by B-S12 and B-P8, suggesting that both mAb induce homodimerization of gp130. Since hematopoietic stem cells express gp130 on their plasma membrane, it was anticipated that the agonistic anti-gp130 mAb could stimulate the proliferation of these stem cells. Indeed, B-S12 and B-P8 were able to stimulate CD34+ cells. In summary, our data show for the first time that mAb against

gp130 can specifically block the action of distinct IL-6-type cytokines that signal through gp130. Such mAb might be of great value for therapeutic applications in diseases where a single cytokine action needs to be inhibited. In addition, the agonistic gp130 mAb may be used as growth factors for maintenance and expansion of stem cells prior to grafting.

MAIN MESH HEADINGS:
Antibodies, Monoclonal/*pharmacology
Antigens, CD/*immunology
*Binding Sites, Antibody
Cytokines/*metabolism
Membrane Glycoproteins/*immunology
Signal Transduction/*immunology

ADDITIONAL MESH HEADINGS:
Animal
Antibodies, Monoclonal/isolation & purification
Antibody Specificity
Antigens, CD/metabolism
Antigens, CD/pharmacology
Cell Division/immunology
Hematopoietic Stem Cells/immunology
Immunoglobulins, Fab/pharmacology
Lymphocyte Transformation
Membrane Glycoproteins/metabolism
Membrane Glycoproteins/pharmacology
Mice
Mice, Inbred BALB C
1995/12
1995/01 00:00

PUBLICATION TYPES:
JOURNAL ARTICLE

CAS REGISTRY NUMBERS:
0 (Antibodies, Monoclonal)
0 (Antigens, CD)
0 (Binding Sites, Antibody)
0 (Cytokines)
0 (Immunoglobulins, Fab)
0 (Membrane Glycoproteins)
133483-10-0 (gp130 signal transducer)

LANGUAGES:
Eng

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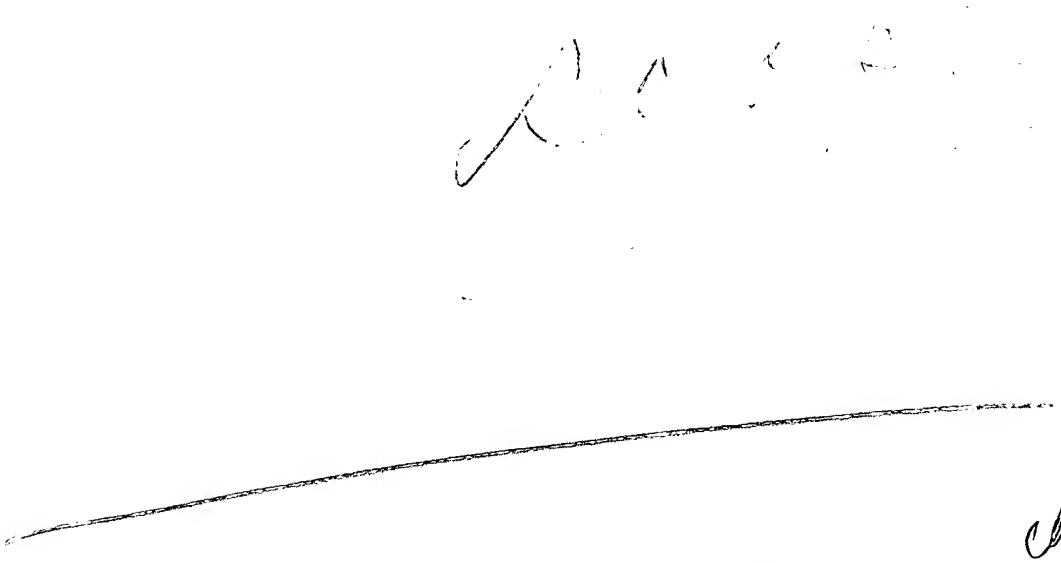
Wijdenes J, et al. Interleukin-6 signal transducer gp130 has specific binding sites for different cytokines as determined by antagonistic and agonistic anti-gp130 monoclonal antibodies. Eur. J. Immunol. Dec. 1995;25(12):3474-81.



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USPT	gp80 with epitope	2	L18
USPT	anti adj gp80	1	L17
USPT	antibod$3 with gp80	14	L16
USPT	antibod with gp80	0	L15
USPT	l13 and cachexia	0	L14
USPT	gp80	28	L13
USPT	l10 not l11	27	L12
USPT	l10 and cachexia	8	L11
USPT	l7 or l8 or l9	35	L10
USPT	anti adj (gp130 or gp80)	13	L9
USPT	antibod$3 adj3 gp80	4	L8
USPT	antibod$3 adj3 gp130	27	L7
USPT	antibod$3 with gp130	45	L6
USPT	l2 and cachexia	10	L5
USPT	anti adj l1	1	L4
USPT	antibod$3 adj5 l1	30	L3
USPT	antibod$3 with l1	48	L2
USPT	(interleukin-6 receptor$1) or (Il-6 receptor) or (Il-6R) or (Il-6 R)	220	L1

Wijdenes et al., "Monoclonal Antibodies (mAb) against gp130 Imitating Cytokines Which Use the gp130 for Signal
Transduction", (Jul. 1995), p. 303.

in limited
studies function-blocking antibodies to IL-6 or IL-6Ra have some efficacy [Klein, et al., Blood 78: 1198-1204
(1991); Suzuki, et al., Eur. J. Immunol. 22:1989-1993 (1992)]. Therefore, IL-6 antagonists as described herein
would be beneficial for both the secondary effects as well as for inhibiting tumor growth.

In fact,
monoclonal antibodies to gp130 inhibit the effects of all of the IL-6 cytokines (Nishimoto et al., J. Exp. Med.
179: 1343-1347 (1994)).

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TITLE:	**Acute mountain sickness--the "poison of the pass".**
AUTHORS:	**Bailey DM**
AUTHOR AFFILIATION:	**University of Glamorgan.**
SOURCE:	**Br J Sports Med 1999 Dec;33(6):376**
CITATION IDS:	**PMID: 10597843 UI: 20064713**
MAIN MESH HEADINGS:	**Altitude Sickness/*prevention & control** **Altitude Sickness/*physiopathology**
ADDITIONAL MESH HEADINGS:	**Acute Disease** **Altitude Sickness/complications** **Cachexia/etiology** **Cachexia/physiopathology** **Female** **Gastrointestinal Diseases/etiology** **Gastrointestinal Diseases/physiopathology** **Human** **Male** **Primary Prevention/methods** **Prognosis** **Respiratory Tract Diseases/etiology** **Respiratory Tract Diseases/physiopathology** **1999/12** **1999/22 09:00**
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LANGUAGES:	**Eng**

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Related Articles

TITLE:	Catabolic proinflammatory cytokines.
AUTHORS:	Argiles JM; Lopez-Soriano FJ
AUTHOR AFFILIATION:	Departament de Bioquimica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Spain. argiles@porthos.bio.ub.es
SOURCE:	Curr Opin Clin Nutr Metab Care 1998 May;1(3):245-51
CITATION IDS:	PMID: 10565356 UI: 20030614
ABSTRACT:	Catabolic proinflammatory cytokines play a key role in mediating biochemical changes associated with many pathophysiological states. The present review emphasizes the role of this type of cytokine in inflammation and cachexia. Additionally, it reviews the role of one of these mediators in the induction of insulin resistance by dealing with some of the most recent publications on this topic.
MAIN MESH HEADINGS:	Cachexia/*physiopathology Cytokines/*physiology Inflammation/*physiopathology
ADDITIONAL MESH HEADINGS:	Animal Arthritis, Rheumatoid/physiopathology Human Insulin Resistance/physiology Obesity/physiopathology Sepsis/physiopathology Shock, Septic/physiopathology 1999/11 1999/24 09:00
PUBLICATION TYPES:	JOURNAL ARTICLE REVIEW REVIEW, TUTORIAL
CAS REGISTRY NUMBERS:	0 (Cytokines)
LANGUAGES:	Eng


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Related Articles | External Links

TITLE:	**[Cockayne syndrome in Lebanon. Description of 3 cases and review of the literature]**
VERNACULAR TITLE:	**Le syndrome de Cockayne au Liban. Description de trois cas et revue de la litterature.**
AUTHORS:	**Jabre P; Mezzina M; Megarbane A**
AUTHOR AFFILIATION:	**Unite de genetique medicale, Faculte de medecine, Universite Saint-Joseph, Beyrouth, Liban.**
SOURCE:	**J Med Liban 1999 Mar-Apr;47(2):144-7**
CITATION IDS:	**PMID: 10410472 UI: 99338661**
ABSTRACT:	**Cockayne syndrome is a rare autosomal recessive progressive neurological disorder characterized by a nanism, a major cachexy, a characteristic facial appearance of premature ageing, a sun-sensitivity, a retinopathy, and a mental retardation. We report three observations of Cockayne syndrome. The diagnostic criteria, notably clinical, found in these patients are discussed in comparison to the literature.**
MAIN MESH HEADINGS:	**Cockayne Syndrome/*diagnosis**
ADDITIONAL MESH HEADINGS:	**Aging, Premature/physiopathology Cachexia/physiopathology Case Report Child Child, Preschool Cockayne Syndrome/genetics Cockayne Syndrome/physiopathology Comparative Study Dwarfism/physiopathology English Abstract Facies Female Genes, Recessive/genetics Human Male Mental Retardation/physiopathology Photosensitivity Disorders/physiopathology**

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1999/07
1999/20 10:00

PUBLICATION TYPES: JOURNAL ARTICLE
REVIEW
REVIEW, TUTORIAL

LANGUAGES: Fre

National Library of Medicine: IGM Full Record Screen

Related Articles | External Links

TITLE: Insights into the pathogenesis of chronic heart failure: immune activation and cachexia.

AUTHORS: Anker SD; Rauchhaus M

AUTHOR AFFILIATION: Department of Cardiac Medicine, National Heart and Lung Institute, London, UK. s.anker@ic.ac.uk

SOURCE: Curr Opin Cardiol 1999 May;14(3):211-6

CITATION IDS: PMID: 10358792 UI: 99286844

ABSTRACT: Body wasting, i.e, cardiac cachexia, is a complication of chronic heart failure (CHF). The authors have suggested that cardiac cachexia should be diagnosed when nonedematous weight loss of more than 7.5% of the premorbid normal weight occurs over a time period of more than 6 months. In an unselected CHF outpatient population, 16% of patients were found to be cachectic. The cachectic state is predictive of poor survival independently of age, functional class, ejection fraction, and exercise capacity. Patients with cardiac cachexia suffer from a general loss of fat, lean, and bone tissue. Cachectic CHF patients are weaker and fatigue earlier. The pathophysiologic causes of body wasting in patients with CHF remain unclear, but initial studies have suggested that humoral neuroendocrine and immunologic abnormalities may be of importance. Cachectic CHF patients show increased plasma levels of catecholamines, cortisol, and aldosterone. Several studies have shown that cardiac cachexia is linked to increased plasma levels of tumor necrosis factor alpha. The degree of body wasting is strongly correlated with neurohormonal and immune abnormalities. Some investigators have suggested that endotoxin may be important in triggering immune activation in CHF patients. Available studies suggest that cardiac cachexia is a multifactorial neuroendocrine and immunologic disorder that carries a poor prognosis. A complex catabolic-anabolic imbalance in different body systems may cause body wasting in patients with CHF.

MAIN MESH HEADINGS: Heart Failure, Congestive/*etiology

ADDITIONAL MESH Cachexia/blood

HEADINGS:	**Cachexia/immunology** **Cachexia/physiopathology** **Chronic Disease** **Heart Failure, Congestive/immunology** **Heart Failure, Congestive/physiopathology** **Human** **Support, Non-U.S. Gov't** **Tumor Necrosis Factor/metabolism** **1999/06** **1999/08 10:00**
PUBLICATION TYPES:	**JOURNAL ARTICLE** **REVIEW** **REVIEW, TUTORIAL**
CAS REGISTRY NUMBERS:	**0 (Tumor Necrosis Factor)**
LANGUAGES:	**Eng**

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Related Articles | External Links

TITLE: The pathophysiology of wasting in the elderly.

AUTHORS: Roubenoff R

AUTHOR AFFILIATION: Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts 02111, USA.

SOURCE: J Nutr 1999 Jan;129(1S Suppl):256S-259S

CITATION IDS: PMID: 9915910 UI: 99115863

ABSTRACT: Aging is associated with changes in body composition and energy and protein metabolism that are due both to the direct effects of aging and to the effect of age-related diseases. We have recently differentiated these changes under three categories: wasting, cachexia, and sarcopenia. We have defined wasting as unintentional loss of weight, including both fat and fat-free compartments. Experience in the HIV epidemic suggests that wasting is driven largely by inadequate dietary intake. Cachexia, on the other hand, refers to loss of fat-free mass, and especially body cell mass, but with little or no weight loss. The metabolic hallmarks of cachexia are hypermetabolism and hypercatabolism, driven by inflammatory cytokine-mediated acute phase responses. Finally, sarcopenia refers to loss of muscle mass specifically, and seems to be an intrinsic age-related condition. In the elderly, wasting as defined here is at the extreme end of the spectrum, but generally develops in the setting of pre-existing sarcopenia and cachexia. The challenges before us now are to better define these conditions, establish guidelines for their recognition, and develop better methods for intervening when appropriate.

MAIN MESH HEADINGS: Wasting Syndrome/*physiopathology

ADDITIONAL MESH HEADINGS:
Aged
Body Composition/physiology
Cachexia/physiopathology
Exertion/physiology
Human
Support, Non-U.S. Gov't

Support, U.S. Gov't, Non-P.H.S.
Support, U.S. Gov't, P.H.S.
Wasting Syndrome/diagnosis
Wasting Syndrome/therapy
1999/01
1999/23 19:27

PUBLICATION TYPES: JOURNAL ARTICLE
REVIEW
REVIEW, TUTORIAL

LANGUAGES: Eng

GRANT/CONTRACT ID: DK45734/DK/NIDDK

National Library of Medicine: IGM Full Record Screen

Related Articles | External Links

TITLE: Visceral leishmaniasis: a model for infection-induced cachexia.

AUTHORS: Pearson RD; Cox G; Jeronimo SM; Castracane J; Drew JS; Evans T; de Alencar JE

AUTHOR AFFILIATION: Department of Medicine, University of Virginia Health Sciences Center, Charlottesville.

SOURCE: Am J Trop Med Hyg 1992 Jul;47(1 Pt 2):8-15

CITATION IDS: PMID: 1632476 UI: 92337090

ABSTRACT: Parasitic infections and malnutrition coexist in many tropical and subtropical areas. Studies of Leishmania donovani and of experimentally infected Syrian hamsters have provided important insights into the complex interrelationships between malnutrition and this parasitic disease. Malnutrition, which adversely affects cell-mediated immunity, is associated with the development of visceral leishmaniasis (kala-azar) in children living in endemic areas. In turn, L. donovani can cause wasting as well as hepatosplenomegaly, fever, and anemia. Syrian hamsters infected with L. donovani develop a disease that is comparable to that of humans with kala-azar. Weight loss in infected hamsters is associated with splenic macrophage secretion of potentially catabolic cytokines as measured by the D10.G4.1 assay for interleukin-1 and the L929 cytotoxicity assay for tumor necrosis factor/cachectin. Although decreased food intake contributes to wasting in infected hamsters, studies of skeletal muscle function indicate that it is not the sole factor. Leishmania donovani-infected hamsters have also been used to study drugs with the potential to prevent or reverse cachexia.

MAIN MESH HEADINGS: Cachexia/*physiopathology
Leishmaniasis, Visceral/*physiopathology

ADDITIONAL MESH HEADINGS: Adipose Tissue
Animal
Brazil

Cachexia/immunology
Child
Child Nutrition Disorders/immunology
Child Nutrition Disorders/physiopathology
Child, Preschool
Disease Models, Animal
Hamsters
Human
Interleukin-1/biosynthesis
Leishmaniasis, Visceral/immunology
Mesocricetus
Nutrition Disorders/immunology
Nutrition Disorders/physiopathology
Protein-Energy Malnutrition/immunology
Protein-Energy Malnutrition/physiopathology
Support, Non-U.S. Gov't
Support, U.S. Gov't, P.H.S.
T-Lymphocytes/immunology
Tumor Necrosis Factor/physiology
1992/07
1992/01 00:00

PUBLICATION TYPES: JOURNAL ARTICLE
REVIEW
REVIEW, TUTORIAL

CAS REGISTRY NUMBERS: 0 (Interleukin-1)
0 (Tumor Necrosis Factor)

LANGUAGES: Eng

GRANT/CONTRACT ID: T32 AI-07046/AI/NIAID
PO1-AI-26512/AI/NIAID

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Related Articles

TITLE: Cachectin/tumor necrosis factor and other cytokines in infectious disease.

AUTHORS: Tracey KJ; Cerami A

AUTHOR AFFILIATION: Department of Neurosurgery, New York Hospital-Cornell University Medical Center.

SOURCE: Curr Opin Immunol 1989 Feb;1(3):454-61

CITATION IDS: PMID: 2679705 UI: 90027230

ABSTRACT: The studies reviewed here represent but a fraction of those published in the field last year, but they serve to illustrate two important points: (1) the cytokine network possesses enormous diversity of biological function, and (2) it is redundant, such that overlapping and synergistic effects are observed between many different cytokines. The impact of this system on the host is pervasive and readily amplifiable, and integrates the diverse responses to infectious disease which may be either beneficial, protecting against infection, or deleterious, causing tissue injury and death. The example of cachectin/TNF illustrates this type of scenario: during local infection or inflammation, low levels of cachectin/TNF act to enhance immune responsiveness, stimulate blood-vessel growth, increase energy mobilization, induce the release of other cytokines, and promote wound-healing; when overwhelming infection occurs, as in septicemia, large quantities of cachectin/TNF reach the circulation and cause shock, MSOF, and death; if a persisting infection develops and cachectin/TNF is chronically secreted, it mediates a state of cachexia which may be fatal. Future studies will undoubtedly advance our understanding of these effects, and that of the other cytokines. The development of novel therapies for inflammation, septic shock, and cachexia may be based on such advances.

MAIN MESH HEADINGS: Infection/*physiopathology
Tumor Necrosis Factor/*physiology

ADDITIONAL MESH HEADINGS: Acquired Immunodeficiency Syndrome/physiopathology
Animal

Biological Factors/physiology
Cachexia/physiopathology
Human
Shock, Septic/immunology
Shock, Septic/physiopathology
1989/02
1989/01 00:00

PUBLICATION TYPES: **JOURNAL ARTICLE**
REVIEW
REVIEW, TUTORIAL

CAS REGISTRY NUMBERS: **0 (Biological Factors)**
0 (Cytokines)
0 (Tumor Necrosis Factor)

LANGUAGES: **Eng**

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☑ ATN 60 ATN 277

Related Articles | External Links

TITLE: Interleukin-6 receptor signaling. I. gp80 and gp130 receptor interaction in the absence of interleukin-6.

AUTHORS: Gaillard JP; Mani JC; Liautard J; Klein B; Brochier J

AUTHOR AFFILIATION: INSERM U. 475, 99, rue Puech-Villa, 34197 Montpellier, Cedex 05 France.

SOURCE: Eur Cytokine Netw 1999 Mar;10(1):43-8

CITATION IDS: PMID: 10210772 UI: 99228628

ABSTRACT: Interleukin-6 (IL-6) is used as a growth factor by various tumor cells. It binds to a gp80 specific receptor (IL-6R) and then to a gp130 transducing chain. Both receptor chains are released as soluble functional proteins which circulate in biological fluids. To study the physiological role of these soluble receptors, both proteins were purified from human plasma and the kinetic constants of equilibria between IL-6 and its natural soluble IL-6R (sIL-6R) and gp130 receptor (sgp130) were measured using surface plasmon resonance analysis. Unexpectedly, natural sIL-6R and natural sgp130 were found to interact (Kd = 2.8 nM) in the absence of IL-6. No interaction was seen between the recombinant soluble receptors or between either natural soluble receptor and its recombinant partner. This binary complex was not due to copurification of IL-6 and was detected in human plasma of healthy donors. It results from either direct interaction between the two natural soluble receptors or indirect binding mediated by a yet unidentified copurified plasma molecule playing the role of an IL-6 antagonist. Once formed, the binary complex was found to be unable to bind IL-6. Soluble gp130 had already been shown to inhibit IL-6 signaling by inactivating the IL-6/IL-6R complex. In addition we show that, in the absence of IL-6, circulating natural sgp130 is able to inhibit directly the circulating sIL-6R that is a strong synergic molecule of IL-6 signaling.

MAIN MESH HEADINGS:
Antigens, CD/*physiology
Interleukin-6/*physiology
Membrane Glycoproteins/*physiology

	Paraproteinemias/*immunology Receptors, Interleukin-6/*physiology
ADDITIONAL MESH HEADINGS:	Antibodies, Monoclonal Antigens, CD/blood Antigens, CD/isolation & purification Electrophoresis, Polyacrylamide Gel Epitopes/analysis Female Human Interleukin-6/pharmacology Membrane Glycoproteins/blood Membrane Glycoproteins/isolation & purification Middle Age Paraproteinemias/blood Protein Binding Receptors, Interleukin-6/blood Receptors, Interleukin-6/isolation & purification Signal Transduction/immunology Support, Non-U.S. Gov't 1999/04 1999/22 02:04
PUBLICATION TYPES:	JOURNAL ARTICLE
CAS REGISTRY NUMBERS:	0 (interleukin-6 receptor alpha) 0 (Antibodies, Monoclonal) 0 (Antigens, CD) 0 (Epitopes) 0 (Interleukin-6) 0 (Membrane Glycoproteins) 0 (Receptors, Interleukin-6) 133483-10-0 (gp130 signal transducer)
LANGUAGES:	Eng

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Related Articles | External Links

TITLE: High-level production of alternatively spliced soluble interleukin-6 receptor in serum of patients with adult T-cell leukaemia/HTLV-I-associated myelopathy.

AUTHORS: Horiuchi S; Ampofo W; Koyanagi Y; Yamashita A; Waki M; Matsumoto A; Yamamoto M; Yamamoto N

AUTHOR AFFILIATION: Departments of Microbiology & Molecular Virology, Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan.

SOURCE: Immunology 1998 Nov;95(3):360-9

CITATION IDS: PMID: 9824498 UI: 99069295

ABSTRACT: We have previously shown, using human T-cell lymphocytotrophic virus-I (HTLV-I)-infected cell lines, that soluble interleukin-6 receptor (sIL-6R) is generated through an alternative splicing mechanism. In this study, we examined human sera for the presence of alternatively spliced soluble IL-6R (AS-sIL-6R). We produced a monoclonal antibody (mAb) recognizing the unique sequence of AS-sIL-6R peptide, generated by an altered reading frame. We also made recombinant AS-sIL-6R protein in Spodoptera frugiperda-9 (Sf-9) cells carrying baculovirus, which encoded altered sIL-6R or conventional IL-6R cDNA. mAbs specifically recognized AS-sIL-6R, but not conventional IL-6R, as demonstrated by Western blot analyses, fluorescence-activated cell sorter, immunofluorescence analyses and enzyme-linked immunosorbent assay (ELISA). We adapted an ELISA system and used it for detection of altered sIL-6R in sera from 23 healthy persons, 12 patients with adult T-cell leukaemia (ATL) and 13 patients with HTLV-I-associated myelopathy (HAM). Serum levels of AS-sIL-6R were 6.4 or 6.1 times greater in ATL (28.7+/-20.4 ng/ml, P<0.0001) and in HAM patients (27.5+/-12.1 ng/ml, P<0.0001) than in healthy individuals (4.5+/-2.1 ng/ml). High levels of AS-sIL-6R were also observed in plasma from rheumatoid arthritis patients and in persons with elevated levels of alanine aminotransferase (ALT), antinuclear antibody (ANA), or alpha-fetoprotein (AFP). However, in human

immunodeficiency virus-1 (HIV-1), hepatitis B virus (HBV) or hepatitis C virus (HCV)-infected individuals, AS-sIL-6R levels were not elevated. In this study, we confirmed that AS-sIL-6R is indeed present in human sera. These observations suggest that alternative splicing of IL-6R mRNA is of consequence in ATL, HAM and in some autoimmune diseases. The HTLV-I-infected T cells appeared to play an important role in AS-sIL-6R production.

MAIN MESH HEADINGS:
*Alternative Splicing
Leukemia, T-Cell/*immunology
Paraparesis, Tropical Spastic/*immunology
Receptors, Interleukin-6/*biosynthesis

ADDITIONAL MESH HEADINGS:
Adult
Antibodies, Monoclonal/immunology
Arthritis, Rheumatoid/immunology
Baculoviridae/genetics
Blotting, Western
Cell Culture
DNA, Complementary/genetics
Enzyme-Linked Immunosorbent Assay
Fluorescent Antibody Technique, Indirect
Human
Receptors, Interleukin-6/blood
Receptors, Interleukin-6/genetics
Recombinant Proteins/biosynthesis
RNA, Messenger/genetics
Solubility
Support, Non-U.S. Gov't
1998/11
1998/21 03:04

PUBLICATION TYPES:
JOURNAL ARTICLE

CAS REGISTRY NUMBERS:
0 (Antibodies, Monoclonal)
0 (DNA, Complementary)
0 (Receptors, Interleukin-6)
0 (Recombinant Proteins)
0 (RNA, Messenger)

LANGUAGES:
Eng

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Related Articles | External Links

TITLE: Analysis of the mechanism of action of anti-human interleukin-6 and anti-human interleukin-6 receptor-neutralising monoclonal antibodies.

AUTHORS: Kalai M; Montero-Julian FA; Brakenhoff JP; Fontaine V; De Wit L; Wollmer A; Brailly H; Content J; Grotzinger J

AUTHOR AFFILIATION: Institut Pasteur de Bruxelles, Departement de Virologie, Belgium.

SOURCE: Eur J Biochem 1997 Nov 1;249(3):690-700

CITATION IDS: PMID: 9395315 UI: 98055693

ABSTRACT: Anti-human interleukin-6 (human IL-6) and anti-human IL-6 receptor (IL-6R)-neutralising monoclonal antibodies (mAbs) are among the most promising human IL-6-specific inhibitors and have been shown to exert short-term beneficial effects in clinical trials. Simultaneous treatment with different anti-human IL-6 or anti-human IL-6R mAbs was recently suggested to be a potent way to inhibit the action of the cytokine in vivo. Although some of these mAbs are already used, their mechanisms of action and the location of their epitopes on the surface of human IL-6 and human IL-6R are still unknown. Here, we analysed the capacity of several anti-human IL-6 and anti-human IL-6R mAbs to inhibit the interaction between human IL-6, human IL-6R, and human glycoprotein 130 (gp130). We mapped the epitopes of several of these mAbs by studying their binding to human IL-6 and human IL-6R mutant proteins. Our results show that several anti-human IL-6 and anti-human IL-6R-neutralising mAbs block the binding between human IL-6 and human IL-6R, whereas others block the binding to gp130. We provide evidence that some of the latter mAbs inhibit interaction with gp130beta1, whereas others interfere with the binding to gp130beta2. Our results suggest that residues included in the C'D' loop of human IL-6R interact with gp130beta2.

MAIN MESH HEADINGS: Antibodies, Monoclonal/*pharmacology
Interleukin-6/*immunology
Receptors, Interleukin-6/*immunology

ADDITIONAL MESH HEADINGS:	**Animal** **Antibodies, Monoclonal/immunology** **Antibodies, Monoclonal/metabolism** **Antigens, CD/metabolism** **Antigens, CD/pharmacology** **Cell Line** **Electrophoresis, Polyacrylamide Gel** **Enzyme-Linked Immunosorbent Assay** **Epitope Mapping** **Human** **Interleukin-6/antagonists & inhibitors** **Interleukin-6/chemistry** **Interleukin-6/genetics** **Interleukin-6/metabolism** **Membrane Glycoproteins/metabolism** **Membrane Glycoproteins/pharmacology** **Mice** **Models, Molecular** **Neutralization Tests** **Precipitin Tests** **Protein Conformation** **Protein Structure, Tertiary** **Receptors, Interleukin-6/antagonists & inhibitors** **Receptors, Interleukin-6/chemistry** **Receptors, Interleukin-6/genetics** **Receptors, Interleukin-6/metabolism** **Support, Non-U.S. Gov't** **1997/12** **1997/12 02:45**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
CAS REGISTRY NUMBERS:	**0 (Antibodies, Monoclonal)** **0 (Antigens, CD)** **0 (Interleukin-6)** **0 (Membrane Glycoproteins)** **0 (Receptors, Interleukin-6)** **133483-10-0 (gp130 signal transducer)**
LANGUAGES:	**Eng**

National Library of Medicine: IGM Full Record Screen

Related Articles | External Links

TITLE:	**Modulation of interleukin-6/interleukin-6 receptor cytokine loop in the treatment of multiple myeloma.**
AUTHORS:	**Chen YH; Shiao RT; Labayog JM; Modi S; Lavelle D**
AUTHOR AFFILIATION:	**Department of Medicine, University of Illinois College of Medicine and VA West Side Medical Center, Chicago, USA.**
SOURCE:	**Leuk Lymphoma 1997 Sep;27(1-2):11-23**
CITATION IDS:	**PMID: 9373192 UI: 98039029**
ABSTRACT:	**Interluekin-6 (IL-6)/IL-6 receptor (IL-6R) play a major role in autocrine/paracrine growth regulation of myeloma cells and are the central mediators for bone destruction and other systemic manifestations of multiple myeloma. Modulation of the IL-6/IL-6R cytokine loop thus represents a rational therapeutic approach. We updated and reviewed the studies on the agents that targeted IL-6/IL-6R modulation and the results of selected clinical trials. Extensive in vitro studies with human myeloma cell lines or primary myeloma explants have shown that components of this cytokine loop could be modulated by various agents, and such modulation is associated with inhibition of myeloma cell growth. The purported mechanisms of action of these agents, down-regulation or neutralization of IL-6 and/or IL-6R and the interruption of IL-6 binding to IL-6R or gp 130 signal transducer, with possible exception for glucocorticoids and specific antibodies, remain to be formally proven. Clinical trials showed largely limited benefits of these agents. Given tumor cell heterogeneity and the complexity of inter-connected cytokine network in vivo, the future emphasis should be on the strategy of combination treatment that would modulate this cytokine loop at multiple sites. Further advances in delineating IL-6 and related cytokine signal transduction pathways should also suggest other targets for therapeutic intervention.**
MAIN MESH HEADINGS:	**Interleukin-6/*physiology Multiple Myeloma/*therapy Receptors, Interleukin-6/*physiology**
ADDITIONAL MESH	**Animal**

HEADINGS:	**Antibodies, Monoclonal/therapeutic use** **Clinical Trials** **Glucocorticoids/therapeutic use** **Human** **Interferons/therapeutic use** **Retinoids/therapeutic use** **Suramin/therapeutic use** **1997/12** **1997/31 23:36**
PUBLICATION TYPES:	**JOURNAL ARTICLE** **REVIEW** **REVIEW, TUTORIAL**
CAS REGISTRY NUMBERS:	**0 (Antibodies, Monoclonal)** **0 (Glucocorticoids)** **0 (Interleukin-6)** **0 (Receptors, Interleukin-6)** **0 (Retinoids)** **145-63-1 (Suramin)** **9008-11-1 (Interferons)**
LANGUAGES:	**Eng**

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Related Articles | External Links

TITLE: Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy.

AUTHORS: Nishimoto N; Sasai M; Shima Y; Nakagawa M; Matsumoto T; Shirai T; Kishimoto T; Yoshizaki K

AUTHOR AFFILIATION: Department of Medical Science I, School of Health and Sport Sciences, Osaka University, Suita-city, Osaka, Japan. norihiro@imed3.med.osaka-u.ac.jp

SOURCE: Blood 2000 Jan 1;95(1):56-61

CITATION IDS: PMID: 10607684 UI: 20076239

ABSTRACT: Castleman's disease, an atypical lymphoproliferative disorder, can be classified into 2 types: hyaline-vascular and plasma cell types according to the histologic features of the affected lymph nodes. The plasma cell type is frequently associated with systemic manifestations and is often refractory to systemic therapy including corticosteroids and chemotherapy, particularly in multicentric form. Dysregulated overproduction of interleukin-6 (IL-6) from affected lymph nodes is thought to be responsible for the systemic manifestations of this disease. Therefore, interference with IL-6 signal transduction may constitute a new therapeutic strategy for this disease. We used humanized anti-IL-6 receptor antibody (rhPM-1) to treat 7 patients with multicentric plasma cell or mixed type Castleman's disease. All patients had systemic manifestations including secondary amyloidosis in 3. With the approval of our institution's ethics committee and the consent of the patients, they were treated with 50 to 100 mg rhPM-1 either once or twice weekly. Immediately after administration of rhPM-1, fever and fatigue disappeared, and anemia as well as serum levels of C-reactive protein (CRP), fibrinogen, and albumin started to improve. After 3 months of treatment, hypergammaglobulinemia and lymphadenopathy were remarkably alleviated, as were renal function abnormalities in patients with amyloidosis. Treatment was well tolerated with only transient leukopenia. Histopathologic examination revealed reduced follicular hyperplasia and vascularity after rhPM-1

	treatment. The pathophysiologic significance of IL-6 in Castleman's disease was thus confirmed, and blockade of the IL-6 signal by rhPM-1 is thought to have potential as a new therapy based on the pathophysiologic mechanism of multicentric Castleman's disease. (Blood. 2000;95:56-61)
MAIN MESH HEADINGS:	Antibodies, Monoclonal/*therapeutic use Giant Lymph Node Hyperplasia/*therapy Receptors, Interleukin-6/*immunology
ADDITIONAL MESH HEADINGS:	Adult Amyloidosis Anemia C-Reactive Protein/metabolism Fatigue Female Fibrinogen/metabolism Giant Lymph Node Hyperplasia/pathology Giant Lymph Node Hyperplasia/physiopathology Human Interleukin-6/blood Male Middle Age Receptors, Interleukin-6/blood Serum Albumin/metabolism Support, Non-U.S. Gov't Time Factors 1999/12 1999/23 09:00
PUBLICATION TYPES:	CLINICAL TRIAL JOURNAL ARTICLE
CAS REGISTRY NUMBERS:	0 (Antibodies, Monoclonal) 0 (Interleukin-6) 0 (Receptors, Interleukin-6) 0 (Serum Albumin) 9001-32-5 (Fibrinogen) 9007-41-4 (C-Reactive Protein)
LANGUAGES:	Eng

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National Library of Medicine: IGM Metathesaurus Information Screen

Information from many elements of a Metathesaurus concept record is shown.
Select the "green light" icon below to add this concept to your search.

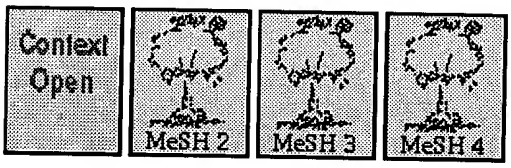
Concept is **Receptors, Interleukin-6**

Definition

Receptors present on T cells, mitogen-activated B cells, peripheral monocytes, and some macrophage- and B cell-derived tumor cell types. The receptor is a strongly glycosylated protein of 80 kD and a length of 468 amino acids. (Ibelgaufts, Dictionary of Cytokines, 1995)

MeSH Tree Context(s)

Selected context is open. Select another context to open it. Each term is a hyperlink. Select it to jump to the equivalent display for that term.



MeSH
}
Chemicals and Drugs (MeSH Category)
}
Amino Acids, Peptides, and Proteins
}
Proteins
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Membrane Proteins
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Receptors, Cell Surface
}
Receptors, Immunologic
}
Receptors, Cytokine
}
Receptors, Interleukin
}
Receptors, Interleukin-6 - Receptors, Interleukin-1 - Receptors

Other Metathesaurus Information

- Qualifiers applied with this concept (4 Kbytes)
- Co-terms applied with this concept (descending frequency, 76 Kbytes)
- Co-terms applied with this concept (alphabetic order, 76 Kbytes)
- Additional MeSH information

Links to Other Database(s)

Images from the History of Medicine

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Related Articles

TITLE: A monoclonal antibody recognizing an epitope shared by receptors for growth hormone, prolactin, interleukin 2 and interleukin 6.

AUTHORS: Longhi SA; Miranda ME; Gobet MG; Retegui LA

AUTHOR AFFILIATION: Instituto de Quimica y Fisicoquimica Biologicas (UBA-CONICET), Facultad de Farmacia y Bioquimica, Buenos Aires, Argentina.

SOURCE: Mol Cell Biochem 1999 May;195(1-2):235-43

CITATION IDS: PMID: 10395088 UI: 99321011

ABSTRACT: Monoclonal antibody (MAb) termed R7B4 was generated throughout the idiotypic-anti-idiotypic network from mice immunized with human and bovine growth hormones (GH). The Ab was selected on the basis that it did not recognize human GH (hGH) neither insolubilized nor in solution but inhibited 125I-hGH binding to receptors from rat and rabbit liver and from Nb2-cell membranes. Since it inhibited Nb2-cell mitogenesis stimulated by hGH, prolactins or placental lactogens, MAb R7B4 behaved as an antagonist of lactogenic hormones. Furthermore, the Ab impaired proliferative activity of interleukin 2 (IL-2) on Nb2 cells as well as growth of 7TD1 cells, an interleukin 6 (IL-6) dependent hybridoma not expressing GH receptors. Biotin-labeled MAb R7B4 specifically bound to rat liver microsomes, and the Ab was able to recognize Nb2 and 7TD1-cell membranes as shown by flow cytometry experiments. However, MAb binding was not hampered by hGH, indicating that the Ab did not mimic GH binding site to receptors. Immunoblot assays indicated that rat and rabbit liver as well as Nb2-cells membrane antigens recognized by MAb R7B4 were similar to those revealed by a MAb directed to prolactin receptors. In addition, MAb R7B4 was able to detect two bands probably corresponding to the somatogenic receptor in rabbit liver microsomes as well as three different proteins in 7TD1-cells showing molecular weights similar to those of the IL-6 receptor complex. Results suggest

that MAb R7B4 is directed to an epitope shared by receptors for lactogenic and somatogenic hormones, IL-2 and IL-6. To our knowledge, these data are the first experimental evidence of the existence of structural similarity between some of the receptors grouped in the cytokine receptor superfamily.

MAIN MESH HEADINGS:
Antibodies, Monoclonal/*metabolism
Epitopes/*immunology
Receptors, Interleukin-2/*immunology
Receptors, Interleukin-6/*immunology
Receptors, Prolactin/*immunology
Receptors, Somatotropin/*immunology

ADDITIONAL MESH HEADINGS:
Animal
Antibodies, Monoclonal/pharmacology
Binding, Competitive
Cattle
Cells, Cultured
Epitopes/metabolism
Flow Cytometry
Human
Hybridomas
Immunization
Immunoblotting
Immunoenzyme Techniques
Insulin/metabolism
Interferons/metabolism
Iodine Radioisotopes/metabolism
Mice
Microsomes, Liver/metabolism
Rats
Receptors, Interleukin-2/metabolism
Receptors, Interleukin-6/metabolism
Receptors, Prolactin/metabolism
Receptors, Somatotropin/metabolism
Sheep
Support, Non-U.S. Gov't
Tumor Cells, Cultured
1999/07
1999/08 10:00

PUBLICATION TYPES:
JOURNAL ARTICLE

CAS REGISTRY NUMBERS:
0 (Antibodies, Monoclonal)
0 (Epitopes)
0 (Iodine Radioisotopes)
0 (Receptors, Interleukin-2)
0 (Receptors, Interleukin-6)
0 (Receptors, Prolactin)
0 (Receptors, Somatotropin)
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☐ **TITLE:** Interleukin-6 directly modulates stem cell factor-dependent development of human mast cells derived from CD34(+) cord blood cells.
Full Citation **AUTHORS:** Kinoshita T, Sawai N, Hidaka E, Yamashita T, Koike K
SOURCE: Blood. 1999 Jul 15;94(2):496-508.
Related Articles **CIT. IDS:** PMID: 10397717 UI: 99326302

☐ **TITLE:** Anticytokine therapy in autoimmune diseases.
Full Citation **AUTHORS:** Nishimoto N, Kishimoto T, Yoshizaki K
SOURCE: Intern Med. 1999 Feb;38(2):178-82. Review.
Related Articles **CIT. IDS:** PMID: 10225680 UI: 99240210

☐ **TITLE:** Blockage of interleukin-6 receptor ameliorates joint disease in murine collagen-induced arthritis.
Full Citation **AUTHORS:** Takagi N, Mihara M, Moriya Y, Nishimoto N, Yoshizaki K, Kishimoto T, Takeda Y, Ohsugi Y
SOURCE: Arthritis Rheum. 1998 Dec;41(12):2117-21.
Related Articles **CIT. IDS:** PMID: 9870868 UI: 99086415

☐ **TITLE:** Therapy of rheumatoid arthritis by blocking IL-6 signal transduction with a humanized anti-IL-6 receptor antibody.
Full Citation **AUTHORS:** Yoshizaki K, Nishimoto N, Mihara M, Kishimoto T
SOURCE: Springer Semin Immunopathol. 1998;20(1-2):247-59. Review. No abstract available.
Related Articles **CIT. IDS:** PMID: 9836380 UI: 99053100

☐ TITLE: IL-6 functions in cynomolgus monkeys blocked by a humanized antibody to human IL-6 receptor.

Full Citation AUTHORS: Imazeki I, Saito H, Hasegawa M, Shinkura H, Kishimoto T, Ohsugi Y

SOURCE: Int J Immunopharmacol. 1998 Jul;20(7):345-57.

Related Articles CIT. IDS: PMID: 9756130 UI: 98427561

☐ TITLE: Signaling through interleukin-6 receptor supports blast cell proliferation in acute myeloblastic leukemia.

Full Citation AUTHORS: Saily M, Koistinen P, Zheng A, Savolainen ER

SOURCE: Eur J Haematol. 1998 Sep;61(3):190-6.

Related Articles CIT. IDS: PMID: 9753415 UI: 98424337

☐ TITLE: Interaction between interleukin 10 and interleukin 6 in human B-cell differentiation.

Full Citation AUTHORS: Bonig H, Packeisen J, Rohne B, Hempel L, Hannen M, Klein-Vehne A, Burdach S, Korholz D

SOURCE: Immunol Invest. 1998 Jul-Sep;27(4-5):267-80.

Related Articles CIT. IDS: PMID: 9730087 UI: 98397824

☐ TITLE: IL-6 receptor blockage inhibits the onset of autoimmune kidney disease in NZB/W F1 mice.

Full Citation AUTHORS: Mihara M, Takagi N, Takeda Y, Ohsugi Y

SOURCE: Clin Exp Immunol. 1998 Jun;112(3):397-402.

Related Articles CIT. IDS: PMID: 9649207 UI: 98311541

☐ TITLE: Human herpesvirus type 8 interleukin-6 homologue is functionally active on human myeloma cells.

Full Citation AUTHORS: Burger R, Neipel F, Fleckenstein B, Savino R, Ciliberto G, Kalden JR, Gramatzki M

SOURCE: Blood. 1998 Mar 15;91(6):1858-63.

Related Articles CIT. IDS: PMID: 9490667 UI: 98158619

☐ TITLE: Inhibition of experimental cancer cachexia by anti-cytokine and anti-cytokine-receptor therapy.

Full Citation AUTHORS: Strassmann G, Kambayashi T

SOURCE: Cytokines Mol Ther. 1995 Jun;1(2):107-13. Review.

Related Articles CIT. IDS: PMID: 9384667 UI: 98029492

☐ TITLE: Analysis of the mechanism of action of anti-human interleukin-6 and anti-human interleukin-6 receptor-neutralising monoclonal antibodies.

Full Citation AUTHORS: Kalai M, Montero-Julian FA, Brakenhoff JP, Fontaine V, De Wit L, Wollmer A, Brailly H, Content J, Grotzinger J

SOURCE: Eur J Biochem. 1997 Nov 1;249(3):690-700.

Related Articles CIT. IDS: PMID: 9395315 UI: 98055693

☐ TITLE: Induction of interleukin-6 (IL-6) autoantibodies through vaccination with an engineered IL-6 receptor antagonist.

Full Citation AUTHORS: Ciapponi L, Maione D, Scoumanne A, Costa P, Hansen MB, Svenson M, Bendtzen K, Alonzi T, Paonessa G, Cortese R, Ciliberto G, Savino R

SOURCE: Nat Biotechnol. 1997 Oct;15(10):997-1001.

Related Articles CIT. IDS: PMID: 9335053 UI: 97475541

☐ TITLE: Interleukin-6: an antagonizing problem becomes a solution.

Full Citation AUTHORS: Rettig MB

SOURCE: Nat Biotechnol. 1997 Oct;15(10):952-3. No abstract available.

Related Articles CIT. IDS: PMID: 9335041 UI: 97475529

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TITLE: Inhibition of experimental cancer cachexia by anti-cytokine and anti-cytokine-receptor therapy.

AUTHORS: Strassmann G; Kambayashi T

AUTHOR AFFILIATION: Department of Immunology, Otsuka-America Pharmaceuticals, Inc, Rockville, MD 20850, USA.

SOURCE: Cytokines Mol Ther 1995 Jun;1(2):107-13

CITATION IDS: PMID: 9384667 UI: 98029492

ABSTRACT: Cachexia consists of a constellation of metabolic changes that occur in cancer patients, including the reduction of muscle and fat tissue, asthenia, anorexia, hypoglycemia and hypercalcemia. These syndromes complicate therapeutic intervention and decrease the quality of life of the patient. This review discusses the involvement of cytokines in cancer cachexia and describes the contribution of IL-6 and other cytokines to the wasting of C-26-bearing mice. The neutralization of IL-6 by antibody, or IL-6 receptor antagonism by suramin, significantly reduce the severity of key parameters of cachexia. The participation of several other factors (PGE2, IL-1, IL-10 and TNF-alpha) in the cellular communication between the C-26 tumor cell and tumor-infiltrating macrophages is also described.

MAIN MESH HEADINGS:
Antibodies/*therapeutic use
Cachexia/*prevention & control
Cytokines/*antagonists & inhibitors
Neoplasms/*physiopathology
Receptors, Cytokine/*antagonists & inhibitors
Suramin/*therapeutic use

ADDITIONAL MESH HEADINGS:
Animal
Cachexia/physiopathology
Cytokines/physiology
Human
Interleukin-6/antagonists & inhibitors
Interleukin-6/physiology
Mice
Mice, Inbred Strains

	Neoplasms, Experimental/physiopathology **Receptors, Cytokine/physiology** **Receptors, Interleukin-6/antagonists & inhibitors** **Receptors, Interleukin-6/physiology** **1997/12** **1997/31 23:39**
PUBLICATION TYPES:	**JOURNAL ARTICLE** **REVIEW** **REVIEW, ACADEMIC**
CAS REGISTRY NUMBERS:	**0 (Antibodies)** **0 (Cytokines)** **0 (Interleukin-6)** **0 (Receptors, Cytokine)** **0 (Receptors, Interleukin-6)** **145-63-1 (Suramin)**
LANGUAGES:	**Eng**

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TITLE: Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy.

AUTHORS: Nishimoto N; Sasai M; Shima Y; Nakagawa M; Matsumoto T; Shirai T; Kishimoto T; Yoshizaki K

AUTHOR AFFILIATION: Department of Medical Science I, School of Health and Sport Sciences, Osaka University, Suita-city, Osaka, Japan. norihiro@imed3.med.osaka-u.ac.jp

SOURCE: Blood 2000 Jan 1;95(1):56-61

CITATION IDS: PMID: 10607684 UI: 20076239

ABSTRACT: Castleman's disease, an atypical lymphoproliferative disorder, can be classified into 2 types: hyaline-vascular and plasma cell types according to the histologic features of the affected lymph nodes. The plasma cell type is frequently associated with systemic manifestations and is often refractory to systemic therapy including corticosteroids and chemotherapy, particularly in multicentric form. Dysregulated overproduction of interleukin-6 (IL-6) from affected lymph nodes is thought to be responsible for the systemic manifestations of this disease. Therefore, interference with IL-6 signal transduction may constitute a new therapeutic strategy for this disease. We used humanized anti-IL-6 receptor antibody (rhPM-1) to treat 7 patients with multicentric plasma cell or mixed type Castleman's disease. All patients had systemic manifestations including secondary amyloidosis in 3. With the approval of our institution's ethics committee and the consent of the patients, they were treated with 50 to 100 mg rhPM-1 either once or twice weekly. Immediately after administration of rhPM-1, fever and fatigue disappeared, and anemia as well as serum levels of C-reactive protein (CRP), fibrinogen, and albumin started to improve. After 3 months of treatment, hypergammaglobulinemia and lymphadenopathy were remarkably alleviated, as were renal function abnormalities in patients with amyloidosis. Treatment was well tolerated with only transient leukopenia. Histopathologic examination revealed reduced follicular hyperplasia and vascularity after rhPM-1

treatment. The pathophysiologic significance of IL-6 in Castleman's disease was thus confirmed, and blockade of the IL-6 signal by rhPM-1 is thought to have potential as a new therapy based on the pathophysiologic mechanism of multicentric Castleman's disease. (Blood. 2000;95:56-61)

MAIN MESH HEADINGS:
Antibodies, Monoclonal/*therapeutic use
Giant Lymph Node Hyperplasia/*therapy
Receptors, Interleukin-6/*immunology

ADDITIONAL MESH HEADINGS:
Adult
Amyloidosis
Anemia
C-Reactive Protein/metabolism
Fatigue
Female
Fibrinogen/metabolism
Giant Lymph Node Hyperplasia/pathology
Giant Lymph Node Hyperplasia/physiopathology
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Interleukin-6/blood
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PUBLICATION TYPES:
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JOURNAL ARTICLE

CAS REGISTRY NUMBERS:
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0 (Interleukin-6)
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